REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-24 are pending. Applicants affirm election of Group I (claims 1-13 and 24) in response to the Examiner's restriction requirement. Non-elected claims 14-23 were withdrawn from consideration by the Examiner. Applicants note that the listing of claim 24 in item 4a) on Form PTO-326 is a mistake.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, she is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

A Form PTO-1449 listing documents cited in the International Search Report was submitted on February 23, 2001. But an initialed copy of the Form PTO-1449 was not returned in the Office Action of January 16, 2002. Applicants request acknowledgment of the Examiner's consideration of the listed documents and return of an initialed copy per MPEP § 609.

Lack of Unity/Election

Applicants note that this application is subject to "lack of unity" practice instead of restriction practice under 35 U.S.C. 371. As discussed below, the claims are linked by a single general inventive concept under PCT Rule 13.1.

The statement on page 2 of the Office Action (i.e., "Applicants further argue that all the compounds recited in claim 1 are Schiff base forming compounds and therefore are not distinct invention") reaches an incorrect conclusion. It was argued that there was unity of invention because all the compounds recited in claim 1 are Schiff base forming compounds. The compound 4-(2-formyl-3-hydroxyphenoxymethyl) benzoic acid was elected in response to the Examiner's requirement for an election of species. Applicants made no statement that selection of an individual species from among the Schiff base forming compounds is not a distinct invention.

Claim 18 directed to manufacture of a medicament has been amended to clarify that it is a method of making the combination recited in claim 24. The latter claim has been amended to overcome the objection stated on page 7 of the Office Action. It is

submitted that claim 18 should be also be examined. Moreover, examining the vaccine composition of claims 14-17 would not constitute an undue burden because the combination of claim 18 has already been examined.

Specification

The drawings were objected to by the Official Draftsperson. Formal drawings with appropriate corrections will be submitted after receipt of a Notice of Allowance.

The Office Action states:

> "The spacing of the lines of the specification is such as to make reading and entry of amendments difficult. New application papers with lines double spaced on good quality paper are required."

Clarification is needed to comply with this requirement. Is the Examiner requesting a new specification or new specification and claims? It is not clear what is being required because "specification" and "application papers" are both used on page 3 of the Office Action. Should the submission contain the amendments made on February 23, 2001 and December 3, 2001, or is a substitute of the original submission needed? Moreover, it is not understood why this requirement is being made because MPEP § 601 states, "The lines of the specification . . . must be 1 ½ or double spaced." Therefore, the use of 1 ½ line spacing in the present specification should be acceptable. Citation of the rule or statute which is the basis for this requirement is respectfully requested.

If the Examiner is not persuaded to withdraw the requirement for a new "specification" or "application papers," Applicants are prepared to submit a copy with double line spacing but clarification of this requirement is requested.

35 U.S.C. 112 – Enablement

Claims 8 and 10 were rejected under Section 112, first paragraph. Applicants traverse.

Regarding the objection to claim 10, the specification on page 21, lines 6-14, describes administration of the adjuvant compound by gene gun including reference to the possible necessity to lyophilise the product and adhere it to gold beads. A person skilled in the art of formulation technology, in particular "gene-gun" or "particulate delivery" administration of molecules, would, given the relative sizes and chemical nature of

both the adjuvant and the desired DNA be able to administer the Schiff base forming compound without undue experimentation from such guidance.

The following articles (abstracts enclosed), provide a small selection of relevant references dealing with this subject as well as the issue of delivery to sites other than the skin, such as the mucosa, in response to the objection to claim 8.

Burkoth et al. (Crit. Rev. Ther. Drug Carrier Syst. 16:331-384, 1999) is a review article which, although it post dates the earliest filing date of the application, reviews high velocity powder injection systems that will facilitate delivery of traditional drugs and oligonucleotides both transdermally and transmucosally. This review describes the configuration and operating principles of devices that accelerate the particles, the properties of the particles and the characteristics of the target tissue. It is therefore clear that by 1999, less than a year after the earliest filing date, individuals were reviewing technology that was readily available and which would facilitate delivery of all kinds of molecules to various parts of the body.

Some of the same authors of the review article discussed above disclosed earlier (Br. Dent. J. 85:536-539, 1998) Oral Powderject, a device for delivering dry powdered anaesthetic (i.e., a traditional drug) to the oral mucosa. This device is the type of device under review in the previous article.

Another reference which post dates the filing date, Chen et al. (Vaccine 19:2908-2917, 2001) describes a Powderject device for delivery of a vaccine with a vaccine adjuvant by epidermal powder immunization. This is further evidence that these "gene gun" devices work on principles that are equally relevant to the delivery of other molecules.

It is therefore clear that at the time of filing the application, the skilled artisan would have been able, without undue experimentation and armed with the disclosure of the specification and in view of the available literature at the time, to administer an adjuvant alone, or combined with a DNA vaccine, to a patient transdermally and to other sites of the body.

Applicants request withdrawal of the Section 112, first paragraph, rejection.

35 U.S.C. 112 – Definiteness

Claim 5 was rejected under Section 112, second paragraph. Applicants traverse.

The phrase 'substantially simultaneous' is not indefinite because the claims have to be read in the context of the specification. By "substantially simultaneous" what is meant is that administration of the compound is preferably at the same time as administration of the DNA sequence, or if not, at least within a few hours either side of DNA sequence administration (page 18, lines 15-18).

Applicants request withdrawal of the Section 112, second paragraph, rejection.

35 U.S.C. 103 – Nonobviousness

Claims 1, 7-9 and 11-13 were rejected under Section 103(a) as allegedly being unpatentable over Rhodes (U.S. Patent 5,508,310) in view of Hermann et al. (U.S. Patent 5,620,896). Applicants traverse.

In contradiction to the Examiner's assertion that Rhodes teaches tucaresol, this compound is expressly excluded from the disclosure in column 2, lines 60-61, of U.S. Patent 5,508,310 as an immunopotentiator however the use of a Schiff-base forming compound as an immunopotentiating agent is disclosed in WO 94/07479. The main focus of the disclosure is the use of such compounds directly in the treatment of viral infections and cancer; the use of such compounds as vaccine adjuvants is mentioned on page 17 of the published PCT specification. This much is stated in the present specification on page 4, lines 8-15. WO 94/07479 only refers to use of immunopotentiators in conjunction with an antigen as in a vaccine employing for example a virus, tumor cells etc. (see page 1 of the published PCT specification). Such use is as a "traditional" vaccine adjuvant by which is meant an adjuvant used with traditional killed or sub-unit vaccines (live vaccines do not require an adjuvant).

It is therefore accepted by Applicants that previous studies show Schiff-base forming compounds such as tucerasol have an immunopotentiating function and that they may therefore act as a conventional adjuvant, with activity comparable to that of the other conventional adjuvants such as alum, Freund's complete adjuvant (FCA) and Freund's incomplete adjuvant (FIA).

However, DNA vaccination uses different mechanisms to achieve their effect in the body, to those of killed or sub-unit vaccines. DNA is incorporated as an episome in the cell and uses the cell's machinery to make protein. Unlike killed or sub-unit vaccines where the antigens of the administered vaccine are broken down and presented to the immune system, DNA vaccines may appear to the immune system much more like a whole live vaccine. Despite being more "live vaccine-like", DNA vaccines do not elicit adequate response alone to be effective. Nonetheless, the need to enhance the immune system when administering DNA vaccines, and the way in which to achieve it, are not disclosed in, nor apparent from the earlier teaching about traditional vaccine adjuvant included in WO 94/07479.

Moreover, known immunopotentiating agents have been tried in combination with DNA vaccines, as disclosed on page 3 lines 27-35, with limited or mixed success and the conventional adjuvants alum, FCA and FIA do not work successfully as adjuvants in DNA vaccination, as demonstrated in Example 1 of the present application. It would therefore be reasonable to assume that conventional adjuvants are ineffective adjuvants for use in DNA vaccination. All the more surprising and unpredictable therefore that Schiff-base forming compounds such as tucaresol, an effective conventional vaccine adjuvant, would have any effect in a DNA vaccine setting. The Examiner is therefore incorrect in citing Rhodes as providing a disclosure that alleges the usefulness of tucaresol in a DNA vaccine setting or even that there would be any motivation to use tucerasol in such a setting with any expectation of success.

Herrmann et al. disclose in column 7, lines 26-30, the desirability of administering or inoculating the DNA transcription unit in the presence of adjuvant or other substances that have the capability of promoting DNA uptake or recruiting immune system cells to the site of inoculation. Hermann et al. do not disclose, however, any particular adjuvants or classes of adjuvants which might be expected to work and provides no working examples using any such adjuvant. Moreover, the purpose of the adjuvant described by Hermann is to promote DNA uptake or recruitment of immune system cells to the site. These might be termed adjuvants by Hermann et al., but they are not the same as agents which would "enhance both humoral and cellular immune responses initiated by the antigenic peptide" as required by the claims of the present invention. This reference

would not therefore provide any additional motivation to that disclosed in Rhodes, and in view of the lack of success reported with conventional adjuvants in enhancing the immune system, no expectation of success can be derived from the disclosure by Hermann of "adjuvants" which are intended to serve a completely different function.

The combined teachings of Rhodes and Hermann would not, therefore, suggest to a person of ordinary skill in the art that tucaresol and its Schiff-base forming cousins will achieve enhancement of the immune response in a DNA vaccine setting, where other conventional adjuvants will not, nor that such compounds will achieve this utility by enhancing both the humoral and cellular immune responses initiated by the antigenic peptide expressed by the nucleotide which forms the DNA vaccine.

Withdrawal of the Section 103 rejection is requested because the invention as claimed was not obvious to a person of ordinary skill in the art at the time it was made.

Conclusion

Applicants acknowledge the objection to claims 2-4, 6 and 24. For the reasons discussed above, claim 1 should be found allowable. But to advance prosecution, claim 24 has been rewritten as an independent claim and the limitations of claim 1 have been incorporated.

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 8), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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Enclosures (three abstracts)

APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

The claims are amended as follows:

14. (Amended) A vaccine composition comprising a nucleotide sequence which encodes for an antigenic peptide associated with a disease state and which is within an appropriate vector, and a Schiff base forming compound which will enhance both humoral and cellular immune responses in a mammal which are initiated by the antigenic peptide, the compound being selected from the group consisting of:

4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;

5-(2-formyl-3-hydroxyphenoxy)pentanamide;

N,*N*-diethyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;

N-isopropyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;

ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;

5-(2-formyl-3-hydroxyphenoxy)pentanonitrile;

(±)-5-(2-formyl-3-hydroxyphenoxy)-2-methylpentanoic acid;

5-(2-formyl-3-hydroxyphenoxy)-2,2-dimethylpentanoic acid;

methyl 3-(2-formyl-3-hydroxyphenoxy)methylbenzoate;

3-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid;

benzyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;

5-[4-(2-formyl-3-hydroxyphenoxy)-*N*-butyl]tetrazole;

7-(2-formyl-3-hydroxyphenoxy)heptanoic acid;

5-(2-formyl-3-hydroxy-4-*n*-propoxyphenoxy)pentanoic acid;

5-(4,6-dichloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(2-formyl-3-hydroxyphenoxy)-*N*-methylsulphonylpentanamide;

ethyl 4-(2-formyl-3-hydroxyphenoxymethyl)benzoate;

5-(4-chloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(3-acetylamino-2-fomyl phenoxy)pentanoic acid;

Aminoguanidine;

4-(2-formyl-3-hydroxyphenoxy)butanoic acid;

6-(2-formyl-3-hydroxyphenoxy)hexanoic acid;

ethyl 4-(3-acetylaminio-2-formylphenoxymethyl)benzoate;

4-(3-acetylamino-2-formylphenoxymethyl)benzoic acid;

2-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;

5-[4-(2-formyl-3-hydroxyphenoxymethyl)phenyl]tetrazole;

5-(2-formyl-3-hydroxy-4-methoxyphenoxy)pentanoic acid;

3-(2-formyl-3-hydroxyphenoxy)propionitrile;

4-Hydroxyphenylacetaldehyde;

Phenylacetaldehyde;

4-Methoxyphenylacetaldehyde;

1-hydroxy-2-phenylpropane;

3-Phenylproponionaldeyde;

4-Nitrobenzaldehyde;

Methyl 4-formylbenzoate;

4-Chlorobenzaldehyde;

4-Methyloxybenzaldehyde;

4-Methylbenzaldehyde;

8,10-Dioxoundecanoic acid;

4,6-Dioxoheptanoic acid;

Pentanedione;

5-methoxy-1-tetralone;

6-methoxy-1-tetralone;

7-methoxy-1-tetralone;

2-tetralone;

3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-butanone;

2' ,4'-dihydroxy-2-(4-methoxyphenyl)acetophenone;

2-hydroxy-1-(4-methyoxyphenyl)-pent-2ene-4one;

Naringenin 4',5,6-trihydroxyflavonone;

4'-methoxy-2-(4-methoxyphenyl)acetophenone;

6,7-dihydroxycoumarin;

7-methoxy-2-tetralone;
6,7-dimethoxy-2-tetralone;
6-hydroxy-4-methylcoumarin;
Homogentisic acid gamma lactone;
6-hydroxy-1,2-naphthoquinone;
8-methoxy-2-tetralone;
[namely] and physiologically acceptable salts thereof, where appropriate.

18. (Amended) A method of making the combination of components according to claim 24, which comprises combining a nucleotide sequence which encodes for [Use of a compound in the manufacture of a medicament, wherein administration of the compound to a mammal enhances both humoral and cellular immune responses initiated by] an antigenic peptide associated with a disease state and a Schiff base forming compound which will enhance both humoral and cellular immune responses initiated by the antigenic peptide, [peptide being expressed as a result of administration to said mammal of a nucleotide sequence encoding for the antigenic peptide;] wherein said compound is selected from the group consisting of:

4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;
5-(2-formyl-3-hydroxyphenoxy)pentanamide;
N,*N*-diethyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;
N-isopropyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;
ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;
5-(2-formyl-3-hydroxyphenoxy)pentanonitrile;
(±)-5-(2-formyl-3-hydroxyphenoxy)-2-methylpentanoic acid;
5-(2-formyl-3-hydroxyphenoxy)-2,2-dimethylpentanoic acid;
methyl 3-(2-formyl-3-hydroxyphenoxy)methylbenzoate;
3-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid;
benzyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;
5-[4-(2-formyl-3-hydroxyphenoxy)-*N*-butyl]tetrazole;
7-(2-formyl-3-hydroxyphenoxy)heptanoic acid;
5-(2-formyl-3-hydroxy-4-*n*-propoxyphenoxy)pentanoic acid;

5-(4,6-dichloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(2-formyl-3-hydroxyphenoxy)-*N*-methylsulphonylpentanamide;

ethyl 4-(2-formyl-3-hydroxyphenoxymethyl)benzoate;

5-(4-chloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(3-acetylamino-2-fomyl phenoxy)pentanoic acid;

Aminoguanidine;

4-(2-formyl-3-hydroxyphenoxy)butanoic acid;

6-(2-formyl-3-hydroxyphenoxy)hexanoic acid;

ethyl 4-(3-acetylaminio-2-formylphenoxymethyl)benzoate;

4-(3-acetylamino-2-formylphenoxymethyl)benzoic acid;

2-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;

5-[4-(2-formyl-3-hydroxyphenoxymethyl)phenyl]tetrazole;

5-(2-formyl-3-hydroxy-4-methoxyphenoxy)pentanoic acid;

3-(2-formyl-3-hydroxyphenoxy)propionitrile;

4-Hydroxyphenylacetaldehyde;

Phenylacetaldehyde;

4-Methoxyphenylacetaldehyde;

1-hydroxy-2-phenylpropane;

3-Phenylproponionaldeyde;

4-Nitrobenzaldehyde;

Methyl 4-formylbenzoate;

4-Chlorobenzaldehyde;

4-Methyloxybenzaldehyde;

4-Methylbenzaldehyde;

8,10-Dioxoundecanoic acid;

4,6-Dioxoheptanoic acid;

Pentanedione;

5-methoxy-1-tetralone;

6-methoxy-1-tetralone;

7-methoxy-1-tetralone;

2-tetralone;

3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-butanone;
2' ,4'-dihydroxy-2-(4-methoxyphenyl)acetophenone;
2-hydroxy-1-(4-methyoxyphenyl)-pent-2ene-4one;
Naringenin 4',5,6-trihydroxyflavonone;
4'-methoxy-2-(4-methoxyphenyl)acetophenone;
6,7-dihydroxycoumarin;
7-methoxy-2-tetralone;
6,7-dimethoxy-2-tetralone;
6-hydroxy-4-methylcoumarin;
Homogentisic acid gamma lactone;
6-hydroxy-1,2-naphthoquinone;
8-methoxy-2-tetralone;
and physiologically acceptable salts thereof, where appropriate.

24. (Amended) A combination of components for separate, sequential or concomitant administration in a method of vaccinating a mammal against a disease state, comprising administrating to said mammal, within an appropriate vector, a nucleotide sequence encoding an antigenic peptide associated with the disease state; additionally administering to said mammal a Schiff base forming compound which enhances both humoral and cellular immune responses initiated by the antigenic peptide, the compound being selected from the group consisting of:
4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;
5-(2-formyl-3-hydroxyphenoxy)pentanamide;
N,N-diethyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;
N-isopropyl 5-(2-formyl-3-hydroxyphenoxy)pentanamide;
ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;
5-(2-formyl-3-hydroxyphenoxy)pentanonitrile;
(±)-5-(2-formyl-3-hydroxyphenoxy)-2-methylpentanoic acid;
5-(2-formyl-3-hydroxyphenoxy)-2,2-dimethylpentanoic acid;
methyl 3-(2-formyl-3-hydroxyphenoxy)methylbenzoate;
3-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid;

benzyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate;

5-[4-(2-formyl-3-hydroxyphenoxy)-*N*-butyl]tetrazole;

7-(2-formyl-3-hydroxyphenoxy)heptanoic acid;

5-(2-formyl-3-hydroxy-4-*n*-propoxyphenoxy)pentanoic acid;

5-(4,6-dichloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(2-formyl-3-hydroxyphenoxy)-*N*-methylsulphonylpentanamide;

ethyl 4-(2-formyl-3-hydroxyphenoxymethyl)benzoate;

5-(4-chloro-2-formyl-3-hydroxyphenoxy)pentanoic acid;

5-(3-acetylamino-2-fomyl phenoxy)pentanoic acid;

Aminoguanidine;

4-(2-formyl-3-hydroxyphenoxy)butanoic acid;

6-(2-formyl-3-hydroxyphenoxy)hexanoic acid;

ethyl 4-(3-acetylaminio-2-formylphenoxymethyl)benzoate;

4-(3-acetylamino-2-formylphenoxymethyl)benzoic acid;

2-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid;

5-[4-(2-formyl-3-hydroxyphenoxymethyl)phenyl]tetrazole;

5-(2-formyl-3-hydroxy-4-methoxyphenoxy)pentanoic acid;

3-(2-formyl-3-hydroxyphenoxy)propionitrile;

4-Hydroxyphenylacetaldehyde;

Phenylacetaldehyde;

4-Methoxyphenylacetaldehyde;

1-hydroxy-2-phenylpropane;

3-Phenylproponionaldeyde;

4-Nitrobenzaldehyde;

Methyl 4-formylbenzoate;

4-Chlorobenzaldehyde;

4-Methyloxybenzaldehyde;

4-Methylbenzaldehyde;

8,10-Dioxoundecanoic acid;

4,6-Dioxoheptanoic acid;

Pentanedione;

5-methoxy-1-tetralone;

6-methoxy-1-tetralone;

7-methoxy-1-tetralone;

2-tetralone;

3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-butanone;

2' ,4'-dihydroxy-2-(4-methoxyphenyl)acetophenone;

2-hydroxy-1-(4-methyoxyphenyl)-pent-2ene-4one;

Naringenin 4',5,6-trihydroxyflavonone;

4'-methoxy-2-(4-methoxyphenyl)acetophenone;

6,7-dihydroxycoumarin;

7-methoxy-2-tetralone;

6,7-dimethoxy-2-tetralone;

6-hydroxy-4-methylcoumarin;

Homogentisic acid gamma lactone;

6-hydroxy-1,2-naphthoquinone;

8-methoxy-2-tetralone;

and physiologically acceptable salts thereof, where appropriate;

wherein the combination comprises [according to claim 1, comprising] the nucleotide sequence encoding for an antigenic peptide and the compound which enhances both humoral and cellular immune responses initiated by the antigenic peptide.

Crit Rev Ther Drug Carrier Syst 1999;16(4):331-84

Transdermal and transmucosal powdered drug delivery.

Burkoth TL, Bellhouse BJ, Hewson G, Longridge DJ, Muddle AG, Sarphie DF.

PowderJect Technologies Inc., Fremont, CA 94555, USA.

High-velocity powder injection is a promising new drug-delivery technique that provides needle- and pain-free delivery of traditional drugs, drugs from biotechnology such as proteins, peptides, and oligonucleotides as well as traditional and genetic vaccines. The energy of a transient helium gas jet accelerates fine drug particles of 20 microns-100 microns diameter to high velocities and delivers them into skin or mucosal sites. This review describes the configuration and operating principles of devices that accelerate the particles, the required properties of the particles, the characteristics of the target tissues, and features of the developmental test methods. Preclinical and clinical results that best characterize the technology and introduce its potential as a drug-delivery platform are presented.

Publication Types:
- Review
- Review, Academic

PMID: 10532199 [PubMed - indexed for MEDLINE]

: Br Dent J 1998 Nov 28;185(10):536-9

Oral PowderJect: a novel system for administering local anaesthetic to the oral mucosa.

Duckworth GM, Millward HR, Potter CD, Hewson G, Burkoth TL, Bellhouse BJ.

Medical Engineering Unit, University of Oxford.

OBJECTIVE: To assess the feasibility of using an Oral PowderJect (OPJ) to safely deliver a dose of dry powdered anaesthetic to the oral mucosa, producing an analgesic effect. DESIGN: Single centre: Part 1. An open, non-randomised safety study to check for mucosal damage; Part 2. A double blind sham controlled study to test the anaesthetic effect. SETTING: General practice. SUBJECTS: Adult, healthy volunteers (4 male, 10 female). MATERIALS AND METHODS: Part 1. An OPJ was used to deliver powdered lidocaine hydrochloride to the mucosal surface which was then checked visually for damage. Part 2. An OPJ containing lidocaine hydrochloride (active) or an empty OPJ (sham) was fired at the oral mucosa. The treated area and an untreated (control) site were probed with the back end of a dental needle. RESULTS: The OPJ delivery caused no visible mucosal damage. The median VAS score for pain on blunt probing was 10 for the OPJ active sites. This was significantly lower than the median VAS score for the sham sites at 30 ($P = 0.0033$) and the control sites at 58 ($P < 0.0001$). CONCLUSIONS: The OPJ can safely deliver powdered lidocaine hydrochloride to the oral mucosa without causing tissue damage. The OPJ delivery of powdered lidocaine hydrochloride can significantly reduce the pain from a blunt needle probe at 1 minute post delivery.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 9874886 [PubMed - indexed for MEDLINE]

Vaccine 2001 Apr 6;19(20-22):2908-17

Adjuvantation of epidermal powder immunization.

Chen D, Erickson CA, Endres RL, Periwal SB, Chu Q, Shu C, Maa YF, Payne LG.

PowderJect Vaccines Inc., 585 Science Drive, Madison, WI 53711, USA.
dexiang_chen@powderject.com

The skin is an immunologically active site and an attractive vaccination route. All current vaccines, however, are administered either orally, intramuscularly, or subcutaneously. We previously reported that epidermal powder immunization (EPI) with an extremely small dose of powdered influenza vaccine induces protective immunity in mice. In this study, we report that commonly used adjuvants can be used in EPI to further enhance the immune responses to an antigen.The IgG antibody response to diphtheria toxoid (DT) following EPI was augmented by 25- and 250-fold, when 1 microg DT was co-delivered with aluminum phosphate (alum) and a synthetic oligonucleotide containing CpG DNA motifs (CpG DNA), respectively. These antibodies had toxin-neutralization activity and were long lasting. Furthermore, EPI using an adjuvant selectively activated different subsets of T helper cells and gave either a Th1 or a Th2 type of immune response. Similar to needle injection into deeper tissues, EPI with alum adsorbed DT promoted a predominantly IgG1 subclass antibody response and elevated level of IL-4 secreting cells. These are indicative of Th2-type immunity. In contrast, co-delivery of CpG DNA adjuvant via EPI led to Th-1 type of response as characterized by the increased production of IgG2a antibodies and IFN-gamma secreting cells. This study indicated that EPI using appropriate adjuvants can produce an augmented antibody response and desirable cellular immune responses. EPI is a promising immunization method that may be used to administer a broad range of vaccines including vaccines with adjuvants.

PMID: 11282202 [PubMed - indexed for MEDLINE]